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(71) Applicant *(for all designated States except US)*: **ALTANA PHARMA AG** [DE/DE]; Byk-Gulden-Str. 2, 78467 Konstanz (DE).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **SIMON, Wolfgang-Alexander** [DE/DE]; Schubertstrasse 17, 78464 Konstanz (DE).

(74) Common Representative: **ALTANA PHARMA AG**; Byk-Gulden-Strasse 2, 78467 Konstanz (DE).

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Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AL, AU, BA, BR, CA, CN, CO, CU, DZ, EC, GE, HR, ID, IL, IN, IS, JP, KR, LT, LV, MA, MK, MX, NO, NZ, PH, PL, SG, TN, UA, VN, YU, ZA, ZW, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR)*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/075926 A1

(54) Title: USE OF PROTON PUMP INHIBITORS FOR THE TREATMENT OF AIRWAY DISORDERS

(57) Abstract: The invention relates to the use of proton pump inhibitors in the treatment of airway disorders.

USE OF PROTON PUMP INHIBITORS FOR THE TREATMENT OF AIRWAY DISORDERS

Technical field

The invention relates to the use of compounds from the class consisting of the acid secretion inhibitors for the treatment of airway disorders.

Prior art

A whole series of compounds are known from the prior art which inhibit gastric acid secretion by blocking the proton pump and which have therefore also been designated as proton pump inhibitors (PPI). These compounds are suitable for the treatment of gastric and intestinal disorders and, accordingly, some of them have been approved by health authorities.

Description of the invention

Surprisingly, it has now been found that the proton pump inhibitors, whose original field of use is the treatment of gastric and intestinal disorders, are particularly suitable for the treatment of airway disorders.

The invention thus relates in a first aspect to the use of proton pump inhibitors in the treatment of airway disorders.

Proton pump inhibitors are designated as those substances which inhibit gastric acid secretion by blocking the proton pump, i.e. substances which bind covalently to the H+/K+-ATPase, the enzyme responsible for gastric acid secretion. These include in particular active compounds having a 2-[(2-pyridinyl)methylsulphinyl]-1H-benzimidazole skeleton or related skeletons, where these skeletons may be substituted in various different ways. The term "proton pump inhibitor" according to the invention comprises not only the active compounds as such, but also their pharmacologically acceptable salts, solvates (in particular hydrates), etc.

Examples of proton pump inhibitors which may be mentioned are those described and claimed in the patent applications and patents below: DE-A-3531487, EP-A-0 005 129, EP-A-0 124 495, EP-A-0 166 287, EP-A 0 174 726, EP-A-0 184 322, EP-A-0 254 588, EP-A-0 261 478, EP-A-0 268 956, EP-A-0 434 999 and WO-A-9523149. Examples which may be mentioned here are the compounds 2-[2-(N-isobutyl-N-methylamino)benzylsulphinyl]benzimidazole (INN: leminoprazole), 2-(4-methoxy-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-ylsulphinyl)-1H-benzimidazole (INN: nepaprazole), 2-(4-methoxy-3-methylpyridin-2-ylmethylsulphinyl)5-pyrrol-1-yl-1H-benzimidazole (IY-81149), 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulphinyl]-1H-imidazo[4,5-b]pyridine (tenatoprazole), especially

5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulphinyl]-1H-benzimidazole (INN: omeprazole), 5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole (INN: esomeprazole), 2-[(3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methylsulphinyl]-1H-benzimidazole (INN: lansoprazole) and 2-{[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]-methylsulphinyl}-1H-benzimidazole (INN: rabeprazole) and in particular 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole (INN: pantoprazole) and (-)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole [INN: (-)-pantoprazole].

The proton pump inhibitors are present as such or in the form of their salts with bases. Examples of salts with bases which may be mentioned are sodium, potassium, magnesium or calcium salts. If the proton pump inhibitors or their salts are isolated in crystalline form, the crystals may contain variable amounts of solvent. Correspondingly, according to the invention, the term "proton pump inhibitor" also includes all solvates, in particular all hydrates, of the proton pump inhibitors and their salts. Particularly preferred salts or hydrates of proton pump inhibitors which may be mentioned are pantoprazole-sodium sesquihydrate (= pantoprazole-sodium x 1.5 H_2O), (-)-pantoprazole-sodium sesquihydrate, pantoprazole-magnesium dihydrate, omeprazole-magnesium, omeprazole-magnesium tetrahydrate, esomeprazole-magnesium and esomeprazole-magnesium tetrahydrate.

Airway disorders to be treated which may be mentioned in particular are pulmonary abnormalities such as bronchitis (including COPD), asthma (particularly night-time asthma attacks), pneumonitis and pulmonary fibrosis.

The invention relates in a further aspect to the use of proton pump inhibitors for the treatment of patients who are suffering from an airway disorder.

The invention further relates to a method for the treatment of airway disorders which consists in administering to a patient who needs such a treatment an effective amount of a proton pump inhibitor.

The invention further relates to the use of proton pump inhibitors for the production of medicaments for the treatment of airway disorders.

The invention further relates to a pharmaceutical preparation for the treatment of airway disorders which contains a proton pump inhibitor as active compound.

The invention further relates to a ready-to-use medicament, comprising a proton pump inhibitor as active compound, which contains a reference to the fact that this ready-to-use medicament can be employed for the treatment of airway disorders.

Commercial utility

According to the invention, the proton pump inhibitors are employed for the treatment of airway disorders in the form of ready-to-use medicaments. These medicaments are prepared by methods known per se and familiar to the person skilled in the art. As medicaments, the proton pump inhibitors are either used here as such, or preferably in combination with suitable pharmaceutical excipients or vehicles in the form of tablets, coated tablets, capsules, suppositories, patches (e.g. as TTS), emulsions, suspensions or solutions, the active compound content advantageously being between 0.1 and 95% and it being possible by means of the appropriate choice of the excipients and vehicles to achieve a pharmaceutical administration form adapted exactly to the active compound and/or to the desired onset of action and/or to the duration of action (e.g. a sustained release form or an enteric form).

The person skilled in the art is familiar on the basis of his/her expert knowledge with which excipients or vehicles are suitable for the desired pharmaceutical formulations. Besides solvents, gel-forming agents, suppository bases, tablet excipients and other active compound carriers, it is possible to use, for example, antioxidants, dispersants, emulsifiers, antifoams, taste corrigents, preservatives, solubilizers, colorants or, in particular, permeation promoters and complexing agents (e.g. cyclodextrins).

The active compounds can be administered orally, parenterally or percutaneously.

In general, it has proved advantageous in human medicine to administer the proton pump inhibitor in a daily dose of, in particular, 0.1 to 1.5 mg/kg of body weight, if appropriate in the form of a number of, preferably 1 to 2, individual doses to achieve the desired result. In the case of a parenteral treatment, similar or (in particular in the case of the intravenous administration of the active compounds) as a rule lower dosages can be used. The determination of the optimal dosage and manner of administration of the active compounds necessary in each case can be carried out easily by any person skilled in the art on the basis of his/her expert knowledge.

The invention further relates to a pharmaceutical preparation for the treatment of airway disorders, which in an individual dose (tablet, capsule, etc.) contains a proton pump inhibitor as active compound in a dose of between 5 and 100, advantageously between 10 and 60, in particular between 20 and 40 mg.

If the proton pump inhibitors are to be employed for the treatment of airway disorders, the pharmaceutical preparations can also contain one or more pharmacologically active constituents of other pharmaceutical groups. Examples which may be mentioned are: tranquillizers (for example from the group consisting of the benzodiazepines, e.g. diazepam), spasmolytics (e.g. bietamiverine or camylofine), anticholinergics (e.g. oxyphencyclimine or phencarbamide), local anaesthetics (e.g. tetracaine or procaine), and optionally also enzymes, vitamins or amino acids.

The combination of the proton pump inhibitors with other pharmaceuticals which are customarily employed for the treatment of airway disorders is to be particularly emphasized in this context.

Patent claims

1. Use of proton pump inhibitors in the treatment of airway disorders.

2. Use of proton pump inhibitors for the treatment of patients who are suffering from an airway disorder.

3. Method for the treatment of airway disorders consisting in that an effective amount of a proton pump inhibitor is administered to a patient who needs such a treatment.

4. Use of proton pump inhibitors for the production of medicaments for the treatment of airway disorders.

5. Pharmaceutical preparation for the treatment of airway disorders, comprising a proton pump inhibitor as active compound.

6. Ready-to-use medicament comprising a proton pump inhibitor as active compound and a reference to the fact that it can be employed for the treatment of airway disorders.

7. Proton pump inhibitor as mentioned in any of Claims 1 to 6, characterized in that it is a compound selected from the group consisting of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl-sulphinyl]-1H-benzimidazole (INN: omeprazole), 5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole (INN: esomeprazole), 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methylsulphinyl]-1H-benzimidazole (INN: lansoprazole) and 2-{[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]-methylsulphinyl}-1H-benzimidazole (INN: rabeprazole) and in particular 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole (INN: pantoprazole) and (-)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole [INN: (-)-pantoprazole] and their pharmacologically acceptable salts.

8. Proton pump inhibitor as mentioned in any of claims 1 to 6, characterized in that it is pantoprazole or a pharmacologically acceptable salt thereof.

9. Airway disorder as mentioned in any of Claims 1 to 6, characterized in that it is bronchitis, COPD, asthma, pneumonitis or pulmonary fibrosis.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/02467

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/454 A61P11/00 A61P11/06 A61P11/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BIOSIS, PAJ, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 97753 A (EISAI CO LTD ;NIECESTRO ROBERT M (US)) 27 December 2001 (2001-12-27) page 6, line 20 -page 7, line 2 page 7, line 24 -page 8, line 2 page 17, line 8 - line 13 ---	1-7,9
X	WO 98 16228 A (PINAS MASSO JOAN ;SERRA CARRERAS JORDI (ES); TROFAST JAN (SE); AST) 23 April 1998 (1998-04-23) page 2, line 4 - line 9 page 7, line 25 - line 29 claims 2,10 --- -/--	1-9

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 May 2003	23/05/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Albrecht, S

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 50037 A (GARVEY DAVID S ;LETTS L GORDON (US); NITROMED INC (US); WANG TIANS) 31 August 2000 (2000-08-31) page 1, line 21 page 5, line 27 claim 15 page 3, line 19 - line 24	1-8
X	US 6 159 968 A (CUPPOLETTI JOHN) 12 December 2000 (2000-12-12) column 1, line 60 -column 2, line 1 column 4, line 50 - line 52 column 14, line 1 - line 6	1-9
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X	ISRAEL D M ET AL: "OMEPRAZOLE AND OTHER PROTON PUMP INHIBITORS: PHARMACOLOGY, EFFICACY AND SAFETY, WITH SPECIAL REFERENCE TO USE IN CHILDREN" JOURNAL OF PEDIATRIC GASTROENTEROLOGY AND NUTRITION, RAVEN PRESS, NEW YORK, NY, US, vol. 5, no. 27, November 1998 (1998-11), pages 568-579, XP008002262 ISSN: 0277-2116 page 575, column 2, paragraph 2 page 575, column 2, paragraph 5 page 576, column 1, paragraph 1	1-7,9
X	MEIER JOHN H ET AL: "Does omeprazole (Prilosec) improve respiratory function in asthmatics with gastroesophageal reflux? A double-blind, placebo-controlled crossover study." DIGESTIVE DISEASES AND SCIENCES, vol. 39, no. 10, 1994, pages 2127-2133, XP001096012 ISSN: 0163-2116 page 2132, paragraph "Conclusions"	1-7,9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/02467

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-3, 7-9 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-6,9 (partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-6,9 (partially)

Present claims 1-6 and 9 relate to a product defined by reference to a desirable characteristic or property, namely proton pump inhibition. The claims cover all products having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the proton pump inhibitors listed individually on pages 1 and 2 of the description.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/02467

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